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(21) International Application Number: PCT/US98/20965 (22) International Filing Date: 6 October 1998 (06.10.98) (30) Priority Data: 08/944,368 6 October 1997 (06.10.97) US (71) Applicant (for all designated States except US): LOYOLA UNIVERSITY OF CHICAGO [US/US]; 820 North Michigan Avenue, Chicago, IL 60611 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): GISSMANN, Lutz [DE/DE]; Pirolweg 1, D-69168 Wiesloch (DE). MÜLLER, Martin [DE/US]; 1351 North Hoyne, Chicago, IL 60622 (US). (74) Agent: WILLIAMS, Joseph, A., Jr.; Marshall, O'Toole, Gerstein, Murray & Borun, 6300 Sears Tower, 233 South Wacker Drive, Chicago, IL 60606-6402 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: PAPILLOMA VIRUS CAPSOMERE VACCINE FORMULATIONS AND METHODS OF USE (57) Abstract Vaccine formulations comprising viral capsomeres are disclosed along with methods for their production. Therapeutic and prophylactic methods of use for the vaccine formulations are also disclosed.		

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PAPILLOMA VIRUS CAPSOMERE VACCINE FORMULATIONS AND METHODS OF USE

FIELD OF THE INVENTION

The present invention relates to vaccine formulations
5 comprising papilloma virus proteins, either as fusion proteins, truncated
proteins, or truncated fusion proteins. The invention further embraces
methods for producing capsomeres of the formulations, as well as
prophylactic and therapeutic methods for their use.

BACKGROUND

10 Infections with certain high-risk strains of genital papilloma
viruses in humans (HPV) -- for example, HPV 16, 18, or 45 -- are
believed to be the main risk factor for the formation of malignant tumors of
the anogenital tract. Of the possible malignancies, cervical carcinoma is by
far the most frequent: according to an estimate by the World Health
15 Organization (WHO), almost 500,000 new cases of the disease occur
annually. Because of the frequency with which this pathology occurs, the
connection between HPV infection and cervical carcinoma has been
extensively examined, leading to numerous generalizations.

For example, precursor lesions of cervical intraepithelial
20 neoplasia (CIN) are known to be caused by papilloma virus infections
[Crum, *New Eng. J. Med.* 310:880-883 (1984)]. DNA from the genomes
of certain HPV types, including for example, strains 16, 18, 33, 35, and
45, have been detected in more than 95% of tumor biopsies from patients
with this disorder, as well as in primary cell lines cultured from the
25 tumors. Approximately 50 to 70% of the biopsied CIN tumor cells have
been found to include DNA derived only from HPV 16.

The protein products of the HPV 16 and HPV 18 early genes
E6 and E7 have been detected in cervical carcinoma cell lines as well as in

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by BPV VLPs. The mouse sera was therefore positive for neutralizing antibodies against the human VLPs and this differential neutralization was most likely the result of antibody specificity for epitopes against which the antibodies were raised.

Numerous modifications and variations in the invention as set forth
5 in the above illustrative examples are expected to occur to those skilled in the art. Consequently only such limitations as appear in the appended claims should be placed on the invention.

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SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:

(ii) TITLE OF INVENTION: Papilloma Virus Capsomere Vaccine Formulations and Methods of Use

(iii) NUMBER OF SEQUENCES: 27

(iv) CORRESPONDENCE ADDRESS:

(A) ADDRESSEE: Marshall, O'Toole, Gerstein, Murray & Borun
 (B) STREET: 233 South Wacker Drive, 6300 Sears Tower
 (C) CITY: Chicago
 (D) STATE: Illinois
 (E) COUNTRY: United States of America
 (F) ZIP: 60606-6402

(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk
 (B) COMPUTER: IBM PC compatible
 (C) OPERATING SYSTEM: PC-DOS/MS-DOS
 (D) SOFTWARE: PatentIn Release #1.0, Version #1.30

(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER:
 (B) FILING DATE:
 (C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:

(A) NAME: Williams Jr., Joseph A.
 (B) REGISTRATION NUMBER: 38,659
 (C) REFERENCE/DOCKET NUMBER: 27013/34028

(ix) TELECOMMUNICATION INFORMATION:

(A) TELEPHONE: 312-474-6300
 (B) TELEFAX: 312-474-0448

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1518 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

(A) NAME/KEY: CDS
 (B) LOCATION: 1..1518

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

ATG	TCT	CTT	TGG	CTG	CCT	AGT	GAG	GCC	ACT	GTC	TAC	TTG	CCT	CCT	GTC	48
Met	Ser	Leu	Trp	Leu	Pro	Ser	Glu	Ala	Thr	Val	Tyr	Leu	Pro	Pro	Val	
1				5				10						15		
CCA	GTA	TCT	AAG	GTT	GTA	AGC	ACG	GAT	GAA	TAT	GTT	GCA	CGC	ACA	AAC	96
Pro	Val	Ser	Lys	Val	Val	Ser	Thr	Asp	Glu	Tyr	Val	Ala	Arg	Thr	Asn	
			20					25					30			

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ATA TAT TAT CAT GCA GGA ACA TCC AGA CTA CTT GCA GTT GGA CAT CCC Ile Tyr Tyr His Ala Gly Thr Ser Arg Leu Leu Ala Val Gly His Pro 35 40 45	144
TAT TTT CCT ATT AAA AAA CCT AAC AAT AAC AAA ATA TTA GTT CCT AAA Tyr Phe Pro Ile Lys Lys Pro Asn Asn Asn Lys Ile Leu Val Pro Lys 50 55 60	192
GTA TCA GGA TTA CAA TAC AGG GTA TTT AGA ATA CAT TTA CCT GAC CCC Val Ser Gly Leu Gln Tyr Arg Val Phe Arg Ile His Leu Pro Asp Pro 65 70 75 80	240
AAT AAG TTT GGT TTT CCT GAC ACC TCA TTT TAT AAT CCA GAT ACA CAG Asn Lys Phe Gly Phe Pro Asp Thr Ser Phe Tyr Asn Pro Asp Thr Gln 85 90 95	288
CGG CTG GTT TGG GCC TGT GTA GGT GTT GAG GTA GGT CGT GGT CAG CCA Arg Leu Val Trp Ala Cys Val Gly Val Glu Val Gly Arg Gly Gln Pro 100 105 110	336
TTA GGT GTG GGC ATT AGT GGC CAT CCT TTA TTA AAT AAA TTG GAT GAC Leu Gly Val Gly Ile Ser Gly His Pro Leu Leu Asn Lys Leu Asp Asp 115 120 125	384
ACA GAA AAT GCT AGT GCT TAT GCA GCA AAT GCA GGT GTG GAT AAT AGA Thr Glu Asn Ala Ser Ala Tyr Ala Ala Asn Ala Gly Val Asp Asn Arg 130 135 140	432
GAA TGT ATA TCT ATG GAT TAC AAA CAA ACA CAA TTG TGT TTA ATT GGT Glu Cys Ile Ser Met Asp Tyr Lys Gln Thr Gln Leu Cys Leu Ile Gly 145 150 155 160	480
TGC AAA CCA CCT ATA GGG GAA CAC TGG GGC AAA GGA TCC CCA TGT ACC Cys Lys Pro Pro Ile Gly Glu His Trp Gly Lys Gly Ser Pro Cys Thr 165 170 175	528
AAT GTT GCA GTA AAT CCA GGT GAT TGT CCA CCA TTA GAG TTA ATA AAC Asn Val Ala Val Asn Pro Gly Asp Cys Pro Pro Leu Glu Leu Ile Asn 180 185 190	576
ACA GTT ATT CAG GAT GGT GAT ATG GTT GAT ACT GGC TTT GGT GCT ATG Thr Val Ile Gln Asp Gly Asp Met Val Asp Thr Gly Phe Gly Ala Met 195 200 205	624
GAC TTT ACT ACA TTA CAG GCT AAC AAA AGT GAA GTT CCA CTG GAT ATT Asp Phe Thr Thr Leu Gln Ala Asn Lys Ser Glu Val Pro Leu Asp Ile 210 215 220	672
TGT ACA TCT ATT TGC AAA TAT CCA GAT TAT ATT AAA ATG GTG TCA GAA Cys Thr Ser Ile Cys Lys Tyr Pro Asp Tyr Ile Lys Met Val Ser Glu 225 230 235 240	720
CCA TAT GGC GAC AGC TTA TTT TTT TAT TTA CGA AGG GAA CAA ATG TTT Pro Tyr Gly Asp Ser Leu Phe Phe Tyr Leu Arg Arg Glu Gln Met Phe 245 250 255	768
GTT AGA CAT TTA TTT AAT AGG GCT GGT GCT GTT GGT GAA AAT GTA CCA Val Arg His Leu Phe Asn Arg Ala Gly Ala Val Gly Glu Asn Val Pro 260 265 270	816
GAC GAT TTA TAC ATT AAA GGC TCT GGG TCT ACT GCA AAT TTA GCC AGT Asp Asp Leu Tyr Ile Lys Gly Ser Gly Ser Thr Ala Asn Leu Ala Ser 275 280 285	864

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TCA Ser 290	AAT Asn	TAT Tyr	TTT Phe	CCT Pro	ACA Thr	CCT Pro	AGT Ser	GGT Gly	TCT Ser	ATG Met	GTT Val	ACC Thr	TCT Ser	GAT Asp	GCC Ala	912
CAA Gln 305	ATA Ile	TTC Phe	AAT Asn	AAA Lys	CCT Pro	TAT Tyr	TGG Trp	TTA Leu	CAA Gln	CGA Arg	GCA Ala	CAG Gln	GGC Gly	CAC His	AAT Asn 320	960
AAT Asn	GGC Gly	ATT Ile	TGT Cys	TGG Trp	GGT Gly	AAC Asn	CAA Gln	CTA Leu	TTT Phe	GTT Val	ACT Thr	GTT Val	GTT Val	GAT Asp	ACT Thr 335	1008
ACA Thr	CGC Arg	AGT Ser	ACA Thr	AAT Asn	ATG Met	TCA Ser	TTA Leu	TGT Cys	GCT Ala	GCC Ala	ATA Ile	TCT Ser	ACT Thr	TCA Ser	GAA Glu	1056
ACT Thr	ACA Thr	TAT Tyr	AAA Lys	AAT Asn	ACT Thr	AAC Asn	TTT Phe	AAG Lys	GAG Glu	TAC Tyr	CTA Leu	CGA Arg	CAT His	GGG Gly	GAG Glu	1104
GAA Glu	TAT Tyr	GAT Asp	TTA Leu	CAG Gln	TTT Phe	ATT Ile	TTT Phe	CAA Gln	CTG Leu	TGC Cys	AAA Lys	ATA Ile	ACC Thr	TTA Leu	ACT Thr	1152
GCA Ala 385	GAC Asp	GTT Val	ATG Met	ACA Thr	TAC Tyr	ATA Ile	CAT His	TCT Ser	ATG Met	AAT Asn	TCC Ser	ACT Thr	ATT Ile	TTG Leu	GAG Glu 400	1200
GAC Asp	TGG Trp	AAT Asn	TTT Phe	GGT Gly	CTA Leu	CAA Gln	CCT Pro	CCC Pro	CCA Pro	GGA Gly	GGC Gly	ACA Thr	CTA Leu	GAA Glu	GAT Asp 415	1248
ACT Thr	TAT Tyr	AGG Arg	TTT Phe	GTA Val	ACC Thr	TCC Ser	CAG Gln	GCA Ala	ATT Ile	GCT Ala	TGT Cys	CAA Gln	AAA Lys	CAT His	ACA Thr	1296
CCT Pro	CCA Pro	GCA Ala	CCT Pro	AAA Lys	GAA Glu	GAT Asp	CCC Pro	CTT Leu	AAA Lys	AAA Lys	TAC Tyr	ACT Thr	TTT Phe	TGG Trp	GAA Glu	1344
GTA Val	AAT Asn	TTA Leu	AAG Lys	GAA Glu	AAG Lys	TTT Phe	TCT Ser	GCA Ala	GAC Asp	CTA Leu	GAT Asp	CAG Gln	TTT Phe	CCT Pro	TTA Leu	1392
GGA Gly	CGC Arg	AAA Lys	TTT Phe	TTA Leu	CTA Leu	CAA Gln	GCA Ala	GGA Gly	TTG Leu	AAG Lys	GCC Ala	AAA Lys	CCA Pro	AAA Lys	TTT Phe 480	1440
ACA Thr	TTA Leu	GGA Gly	AAA Lys	CGA Arg	AAA Lys	GCT Ala	ACA Thr	CCC Pro	ACC Thr	ACC Thr	TCA Ser	TCT Ser	ACC Thr	TCT Ser	ACA Thr	1488
ACT Thr	GCT Ala	AAA Lys	CGC Arg	AAA Lys	AAA Lys	CGT Arg	AAG Lys	CTG Leu	TAA *							1518

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 506 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```

Met Ser Leu Trp Leu Pro Ser Glu Ala Thr Val Tyr Leu Pro Pro Val
 1           5           10           15
Pro Val Ser Lys Val Val Ser Thr Asp Glu Tyr Val Ala Arg Thr Asn
          20           25           30
Ile Tyr Tyr His Ala Gly Thr Ser Arg Leu Leu Ala Val Gly His Pro
          35           40           45
Tyr Phe Pro Ile Lys Lys Pro Asn Asn Asn Lys Ile Leu Val Pro Lys
          50           55           60
Val Ser Gly Leu Gln Tyr Arg Val Phe Arg Ile His Leu Pro Asp Pro
          65           70           75           80
Asn Lys Phe Gly Phe Pro Asp Thr Ser Phe Tyr Asn Pro Asp Thr Gln
          85           90           95
Arg Leu Val Trp Ala Cys Val Gly Val Glu Val Gly Arg Gly Gln Pro
          100          105          110
Leu Gly Val Gly Ile Ser Gly His Pro Leu Leu Asn Lys Leu Asp Asp
          115          120          125
Thr Glu Asn Ala Ser Ala Tyr Ala Ala Asn Ala Gly Val Asp Asn Arg
          130          135          140
Glu Cys Ile Ser Met Asp Tyr Lys Gln Thr Gln Leu Cys Leu Ile Gly
          145          150          155          160
Cys Lys Pro Pro Ile Gly Glu His Trp Gly Lys Gly Ser Pro Cys Thr
          165          170          175
Asn Val Ala Val Asn Pro Gly Asp Cys Pro Pro Leu Glu Leu Ile Asn
          180          185          190
Thr Val Ile Gln Asp Gly Asp Met Val Asp Thr Gly Phe Gly Ala Met
          195          200          205
Asp Phe Thr Thr Leu Gln Ala Asn Lys Ser Glu Val Pro Leu Asp Ile
          210          215          220
Cys Thr Ser Ile Cys Lys Tyr Pro Asp Tyr Ile Lys Met Val Ser Glu
          225          230          235          240
Pro Tyr Gly Asp Ser Leu Phe Phe Tyr Leu Arg Arg Glu Gln Met Phe
          245          250          255
Val Arg His Leu Phe Asn Arg Ala Gly Ala Val Gly Glu Asn Val Pro
          260          265          270
Asp Asp Leu Tyr Ile Lys Gly Ser Gly Ser Thr Ala Asn Leu Ala Ser
          275          280          285
Ser Asn Tyr Phe Pro Thr Pro Ser Gly Ser Met Val Thr Ser Asp Ala
          290          295          300

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Gln Ile Phe Asn Lys Pro Tyr Trp Leu Gln Arg Ala Gln Gly His Asn
 305 310 315 320
 Asn Gly Ile Cys Trp Gly Asn Gln Leu Phe Val Thr Val Val Asp Thr
 325 330 335
 Thr Arg Ser Thr Asn Met Ser Leu Cys Ala Ala Ile Ser Thr Ser Glu
 340 345 350
 Thr Thr Tyr Lys Asn Thr Asn Phe Lys Glu Tyr Leu Arg His Gly Glu
 355 360 365
 Glu Tyr Asp Leu Gln Phe Ile Phe Gln Leu Cys Lys Ile Thr Leu Thr
 370 375 380
 Ala Asp Val Met Thr Tyr Ile His Ser Met Asn Ser Thr Ile Leu Glu
 385 390 395 400
 Asp Trp Asn Phe Gly Leu Gln Pro Pro Pro Gly Gly Thr Leu Glu Asp
 405 410 415
 Thr Tyr Arg Phe Val Thr Ser Gln Ala Ile Ala Cys Gln Lys His Thr
 420 425 430
 Pro Pro Ala Pro Lys Glu Asp Pro Leu Lys Lys Tyr Thr Phe Trp Glu
 435 440 445
 Val Asn Leu Lys Glu Lys Phe Ser Ala Asp Leu Asp Gln Phe Pro Leu
 450 455 460
 Gly Arg Lys Phe Leu Leu Gln Ala Gly Leu Lys Ala Lys Pro Lys Phe
 465 470 475 480
 Thr Leu Gly Lys Arg Lys Ala Thr Pro Thr Thr Ser Ser Thr Ser Thr
 485 490 495
 Thr Ala Lys Arg Lys Lys Arg Lys Leu *
 500 505

(2) INFORMATION FOR SEQ ID NO:3:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 297 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..297

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

ATG CAT GGA GAT ACA CCT ACA TTG CAT GAA TAT ATG TTA GAT TTG CAA	48
Met His Gly Asp Thr Pro Thr Leu His Glu Tyr Met Leu Asp Leu Gln	
1 5 10 15	
CCA GAG ACA ACT GAT CTC TAC TGT TAT GAG CAA TTA AAT GAC AGC TCA	96
Pro Glu Thr Thr Asp Leu Tyr Cys Tyr Glu Gln Leu Asn Asp Ser Ser	
20 25 30	

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GAG GAG GAG GAT GAA ATA GAT GGT CCA GCT GGA CAA GCA GAA CCG GAC	144
Glu Glu Glu Asp Glu Ile Asp Gly Pro Ala Gly Gln Ala Glu Pro Asp	
35 40 45	
AGA GCC CAT TAC AAT ATT GTA ACC TTT TGT TGC AAG TGT GAC TCT ACG	192
Arg Ala His Tyr Asn Ile Val Thr Phe Cys Cys Lys Cys Asp Ser Thr	
50 55 60	
CTT CGG TTG TGC GTA CAA AGC ACA CAC GTA GAC ATT CGT ACT TTG GAA	240
Leu Arg Leu Cys Val Gln Ser Thr His Val Asp Ile Arg Thr Leu Glu	
65 70 75 80	
GAC CTG TTA ATG GGC ACA CTA GGA ATT GTG TGC CCC ATC TGT TCT CAG	288
Asp Leu Leu Met Gly Thr Leu Gly Ile Val Cys Pro Ile Cys Ser Gln	
85 90 95	
AAA CCA TAA	297
Lys Pro *	

(2) INFORMATION FOR SEQ ID NO:4:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 98 amino acids
 - (B) TYPE: amino acid
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Met His Gly Asp Thr Pro Thr Leu His Glu Tyr Met Leu Asp Leu Gln	
1 5 10 15	
Pro Glu Thr Thr Asp Leu Tyr Cys Tyr Glu Gln Leu Asn Asp Ser Ser	
20 25 30	
Glu Glu Glu Asp Glu Ile Asp Gly Pro Ala Gly Gln Ala Glu Pro Asp	
35 40 45	
Arg Ala His Tyr Asn Ile Val Thr Phe Cys Cys Lys Cys Asp Ser Thr	
50 55 60	
Leu Arg Leu Cys Val Gln Ser Thr His Val Asp Ile Arg Thr Leu Glu	
65 70 75 80	
Asp Leu Leu Met Gly Thr Leu Gly Ile Val Cys Pro Ile Cys Ser Gln	
85 90 95	
Lys Pro *	

(2) INFORMATION FOR SEQ ID NO:5:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 34 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

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CCCCGATATC GCCTTTAATG TATAAATCGT CTGG

34

(2) INFORMATION FOR SEQ ID NO:6:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 35 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

CCCCGATATC TCAAATTATT TTCCTACACC TAGTG

35

(2) INFORMATION FOR SEQ ID NO:7:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 40 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

AAAGATATCT TGTAATAAAA ATTTGCGTCC TAAAGGAAAC

40

(2) INFORMATION FOR SEQ ID NO:8:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 44 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

AAAGATATCT AATCTACCTC TACAACTGCT AAACGCAAAA AACG

44

(2) INFORMATION FOR SEQ ID NO:9:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 35 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

AAAAGATATC ATGCATGGAG ATACACCTAC ATTGC

35

(2) INFORMATION FOR SEQ ID NO:10:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 34 base pairs

- 35 -

- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

TTTTGATATC GGCTCTGTCC GGTTCCTGCTT GTCC

34

(2) INFORMATION FOR SEQ ID NO:11:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 44 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

TTTTGATATC CTTGCAACAA AAGGTTACAA TATTGTAATG GGCC

44

(2) INFORMATION FOR SEQ ID NO:12:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 35 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

AAAAGATATC TGGTTTCTGA GAACAGATGG GGCAC

35

(2) INFORMATION FOR SEQ ID NO:13:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 38 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

TTTTGATATC GATTATGAGC AATTAAATGA CAGCTCAG

38

(2) INFORMATION FOR SEQ ID NO:14:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 35 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

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TTTTGATATC GTCTACGTGT GTGCTTTGTA CGCAC

35

(2) INFORMATION FOR SEQ ID NO:15:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 39 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

TTTATCGATA TCGGTCCAGC TGGACAAGCA GAACCGGAC

39

(2) INFORMATION FOR SEQ ID NO:16:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 39 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

TTTTGATATC GATGCCCATTT ACAATATTGT AACCTTTTG

39

(2) INFORMATION FOR SEQ ID NO:17:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 294 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..294

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

ATG	AGT	CTT	CTA	ACC	GAG	GTC	GAA	ACG	CTT	ACC	AGA	AAC	GGA	TGG	GAG	48
Met	Ser	Leu	Leu	Thr	Glu	Val	Glu	Thr	Leu	Thr	Arg	Asn	Gly	Trp	Glu	
1				5					10					15		
TGC	AAA	TGC	AGC	GAT	TCA	AGT	GAT	CCT	CTC	ATT	ATC	GCA	GCG	AGT	ATC	96
Cys	Lys	Cys	Ser	Asp	Ser	Ser	Asp	Pro	Leu	Ile	Ile	Ala	Ala	Ser	Ile	
			20					25					30			
ATT	GGG	ATC	TTG	CAC	TTG	ATA	TTG	TGG	ATT	TTT	TAT	CGT	CTT	TTC	TTC	144
Ile	Gly	Ile	Leu	His	Leu	Ile	Leu	Trp	Ile	Phe	Tyr	Arg	Leu	Phe	Phe	
			35				40					45				
AAA	TGC	ATT	TAT	CGT	CGC	CTT	AAA	TAC	GGT	TTG	AAA	AGA	GGG	CCT	TCT	192
Lys	Cys	Ile	Tyr	Arg	Arg	Leu	Lys	Tyr	Gly	Leu	Lys	Arg	Gly	Pro	Ser	
	50					55					60					

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ACG GAA GGA GCG CCT GAG TCT ATG AGG GAA GAA TAT CGG CAG GAA CAG 240
 Thr Glu Gly Ala Pro Glu Ser Met Arg Glu Glu Tyr Arg Gln Glu Gln 80
 65 70 75
 CAG AGT GCT GTG GAT GTT GAC GAT GTT CAT TTT GTC AAC ATA GAG CTG 288
 Gln Ser Ala Val Asp Val Asp Asp Val His Phe Val Asn Ile Glu Leu 95
 85 90
 GAG TAA 294
 Glu *

(2) INFORMATION FOR SEQ ID NO:18:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 97 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Met Ser Leu Leu Thr Glu Val Glu Thr Leu Thr Arg Asn Gly Trp Glu
 1 5 10 15
 Cys Lys Cys Ser Asp Ser Ser Asp Pro Leu Ile Ile Ala Ala Ser Ile
 20 25 30
 Ile Gly Ile Leu His Leu Ile Leu Trp Ile Phe Tyr Arg Leu Phe Phe
 35 40 45
 Lys Cys Ile Tyr Arg Arg Leu Lys Tyr Gly Leu Lys Arg Gly Pro Ser
 50 55 60
 Thr Glu Gly Ala Pro Glu Ser Met Arg Glu Glu Tyr Arg Gln Glu Gln
 65 70 75 80
 Gln Ser Ala Val Asp Val Asp Asp Val His Phe Val Asn Ile Glu Leu
 85 90 95
 Glu *

(2) INFORMATION FOR SEQ ID NO:19:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 40 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

TTTTGATATC GATATGGAAT GGCTAAAGAC AAGACCAATC

40

(2) INFORMATION FOR SEQ ID NO:20:

- (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 35 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single

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(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

TTTTGATATC GTTGTGTTGGA TCCCCATTCC CATTG 35

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

GTTATGACAT ACATACATTC TATG 24

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 35 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

CCATGCATTC CTGCTTGTAG TAAAAATTTG CGTCC 35

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 29 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

CTACAAGCAG GAATGCATGG AGATACACC 29

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 36 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

CATCTGAAGC TTAGTAATGG GCTCTGTCCG GTTCTG 36

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(2) INFORMATION FOR SEQ ID NO:25:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 38 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

CATCTGAAGC TTATCAATAT TGTAATGGGC TCTGTCCG

38

(2) INFORMATION FOR SEQ ID NO:26:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 54 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

CATCTGAAGC TTAAGGCTTA CAAAAGGTTA CAATATTGTA ATGGGCTCTG TCCG

54

(2) INFORMATION FOR SEQ ID NO:27:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 69 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

CATCTGAAGC TTAAAGCGTA GAGTCACACT TGCAACAAAA GGTACAATA TTGTAATGGG

60

CTCTGTCCG

69

(2) INFORMATION FOR SEQ ID NO:28:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 47 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

CATCTGAAGC TTATTGTACG CACAACCGAA GCGTAGAGTC AACTTG

47

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WHAT IS CLAIMED IS:

1. A vaccine formulation comprising a human papilloma virus capsomere, said capsomere comprising a fusion protein comprising a human papilloma virus L1 protein adjacent amino acid residues from a second protein.
2. A vaccine formulation comprising a human papilloma virus capsomere, said capsomere comprising a truncated human papilloma virus L1 protein having a deletion of one or more amino acid residues necessary for formation of a virus-like particle.
3. The vaccine formulation of claim 2 wherein said capsomere comprises a fusion protein comprising a truncated human papilloma virus L1 protein adjacent amino acid residues from a second protein.
4. The vaccine formulation of any one of claims 1, 2, or 3 wherein the L1 protein is encoded in the genome of a human papilloma virus selected from the group consisting of HPV6, HPV11, HPV16, HPV18, HPV33, HPV35, and HPV45.
5. The vaccine formulation of claim 4 wherein the papilloma virus is HPV16.
6. The vaccine formulation of any one of claims 2, 3, or 5 wherein carboxy terminal amino acid residues are deleted from the L1 protein.
7. The vaccine formulation of claim 6 wherein 1 to 34 carboxy terminal amino acid residues are deleted from the L1 protein.

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8. The vaccine formulation of claim 7 wherein 34 carboxy terminal amino acid residues are deleted from the L1 protein.

9. The vaccine formulation of any one of claims 2, 3, or 5 wherein amino terminal amino acid residues are deleted from the L1 protein.

10. The vaccine formulation of any one of claims 2, 3, or 5 wherein internal amino acid residues are deleted from the L1 protein.

11. The vaccine formulation of claim 10 wherein the amino acid residues deleted from the L1 protein comprise a nuclear localization signal.

12. The vaccine formulation of claims 2 or 3 wherein the amino acids residues from the second protein are derived from an HPV protein.

13. The vaccine formulation of claim 12 wherein the HPV protein is an early HPV protein.

14. The vaccine formulation of claim 12 wherein the early HPV protein is selected from the group consisting of E1, E2, E3, E4, E5, E6, and E7.

15. A method of treating an individual infected with an HPV virus comprising the step of administering to a patient in need thereof an amount of the vaccine formulation of claims 1, 2, 3, 5, 7, 8, 11, 13 or 14 effective to reduce the level of HPV infection.

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16. A method for preventing papilloma virus infection comprising the step of administering to an individual susceptible thereto an amount of the vaccine formulation of claims 1, 2, 3, 5, 7, 8, 11, 13 or 14 effective to inhibit HPV infection.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/20965

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/62 A61K39/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
----------	--	-----------------------

X

MÜLLER M ET AL.: "Chimeric papillomavirus-like particles" VIROLOGY, vol. 234, no. 1, 21 July 1997, pages 93-111, XP002091857 ORLANDO US see the whole document

1-8,
10-16

X

DE 44 35 907 A (GISSMANN L;ZHOU J; MÜLLER M) 11 April 1996 see the whole document

1-5,
10-16

-/--

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"g" document member of the same patent family

Date of the actual completion of the international search

1 February 1999

Date of mailing of the international search report

16/02/1999

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Authorized officer

Cupido, M

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/20965

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>LI M ET AL.: "Expression of the human papillomavirus type 11 L1 capsid protein in Escherichia coli" JOURNAL OF VIROLOGY, vol. 71, no. 4, April 1997, pages 2988-2995, XP002091858 AMERICAN SOCIETY FOR MICROBIOLOGY US see figure 7</p>	1-4,9
A	<p>PAINTSIL J ET AL.: "Carboxy terminus of bovine papillomavirus type-1 L1 protein is not required for capsid formation" VIROLOGY, vol. 223, no. 1, 1 September 1996, pages 238-244, XP002091859 ORLANDO US see figure 1</p>	1-16
A	<p>ROSE R C ET AL: "SEROLOGICAL DIFFERENTIATION OF HUMAN PAPILLOMAVIRUS TYPES 11, 16 AND 18 USING RECOMBINANT VIRUS-LIKE PARTICLES" JOURNAL OF GENERAL VIROLOGY, vol. 75, no. 9, September 1994, pages 2445-2449, XP000604635</p>	1-16
A	<p>WO 96 11274 A (US DEPARTMENT OF HEALTH) 18 April 1996 see examples 1-7</p>	1-16

INTERNATIONAL SEARCH REPORT

national application No.

PCT/US 98/20965

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 15 and 16
are directed to a method of treatment of the human or animal
body, the search has been carried out and based on the alleged
effects of the vaccine formulation.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/20965

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 4435907 A	11-04-1996	AU 4270196 A	02-05-1996
		CA 2202090 A	18-04-1996
		WO 9611272 A	18-04-1996
		EP 0809700 A	03-12-1997
WO 9611274 A	18-04-1996	US 5618536 A	08-04-1997
		AU 3828495 A	02-05-1996
		EP 0789766 A	20-08-1997
		JP 10506796 T	07-07-1998
		US 5855891 A	05-01-1999

